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TITLE: Modulating Calcium Signals to Boost AON Exon Skipping for DMD

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CONTRACTING ORGANIZATION:

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14. ABSTRACT

AON-mediated exon skipping is currently advancing as therapy for DMD, though levels of dystrophin produced remains suboptimal. Thus, identification of compounds with the capacity to boost exon skipping could help fully realize this potentially life-changing DMD treatment. We have assessed whether dantrolene, an already FDA-approved drug, can boost efficacy of AON exon skipping in the context of AON targeting skipping of exons 51, 44 or 45. Additionally, we have begun testing proprietary compounds that regulate the same Ca2+ pathway regulated by dantrolene for skip-boosting. . As a second objective we are assessing these compounds for their ability promote exon skipping in patient cells with DMD mutations that have a low level endogenous skipping, dystrophin expression and/or mild phenotypes. Preliminary data indicate that these compounds are effective in at least a subset of patient cell models; one candidate may boost skipping even better than dantrolene. Based on its known activity, this compound promises greater efficacy and a wider therapeutic window than dantrolene. Planned studies will combine chemical genomics with RNA Seq analysis to identify mechanisms of activity and specificity in order to guide discovery of second-generation skipping drugs or combinations with greater activity.

15. SUBJECT TERMS

Exon skipping, Dantrolene, Calcium, Duchenne, Dytrophy, Dystrophin, anti-sense-oligonucleatide, DMD, RNA therapeutics.

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1. INTRODUCTION

AON-AON-mediated exon skipping is currently advancing as therapy for DMD, though levels of dystrophin produced remain suboptimal. Thus, identification of compounds with the capacity to boost AON-directed exon skipping may help fully realize this potentially life-changing treatment for DMD. Here, we will assess whether dantrolene, an FDA-approved drug already demonstrated to boost efficacy of AON exon skipping in the context of e45-50 DMD deletions, is also relevant to other mutations amenable to exon 51 skipping or to other exon 44, 45 or 53 AON/DMD mutation skip combinations currently in the clinical trial pipeline.
Additionally, we will test the two proprietary compounds that regulate the same Ca2+ pathway regulated by dantrolene for their activity in boosting AON-directed exon 51, 44, 45, or 53 skipping. Based on their known activity, these compounds promise greater efficacy and a wider therapeutic window than dantrolene. As a second objective we will assess the ability of these compounds to promote exon skipping in patient cells with *DMD* mutations that have a propensity for low level endogenous skipping, dystrophin expression and/or mild phenotypes. We hypothesize that these compounds may promote skipping in the absence of AON, and thus would represent a cost effective alternative to AON skipping for a subset of very rare mutations. Finally, we hypothesize that by combining chemical genomics with RNA Seq analysis we can begin to identify mechanisms of compound activity and specificity in order to guide second-generation drug discovery.

2. KEYWORDS

Exon skipping, dantrolene, Calcium, Duchenne, Dystrophy, dystrophin, anti-sense-oligonucleatide, DMD

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1:
Major Task 1 – Testing RyR pathway antags on DMD patient cells with e51, e45, e44 and e53 skippable mutations

Subtask 1 - Develop skipping conditions and readouts for skipping exons 44, 45 and 53 in patient derived cells (6 months; 90% complete).

This task has been largely completed for exons 44 and 45 and are described in Figures 1 and 2. We have begun to assess exon 53 skip conditions but have yet to utilize them routinely.

Subtask 2 - Test compounds on 51, 44, 45 and 53 skippable cells for activity in combination with AON. Search for sequence motifs in intron/exons that correlate with compound activity (6-36 months; 50% complete).

We have previously demonstrated that RyR antags can boost AON directed exon 51 skipping in patient derived iDRM. Assessment of additional exon51 skippable patient cells are underway.

To assess conditions for boost activity on skipping DMD mutations rendered in frame by exon 45 skipping, we ran a dose escalation (125, 250, 500 or 1000nM of E45AO) with or without Dantrolene 50nM (previously Kendall et al 2012) to determine best boosted AON concentration. 500nM AON was used in subsequent assays with or without drugs at indicated concentrations. Fig 1 demonstrates that all three RyRantags boost AON H45A (AON) (Wilton et al 2007) exon 45 skipping in DRMCDMD1003 (delta 46-51) in a dose dependant way. Figure 2 demonstrates that AON mediated exon 44 skipping is also boosted by RyRCal2 in patient CDMD1015iDRM. While boost is modest, we anticipate a greater boot with lower AON concentrations. Additional iDRM testing and dosing is under way to determine weather all exon 45, 44 or 51 skips can be boosted. Early results indicate that a second exon 45 skippable DMD iDRMCD45 is boosted similarly. We have yet to begin assessing activity on 53 skippable cells.

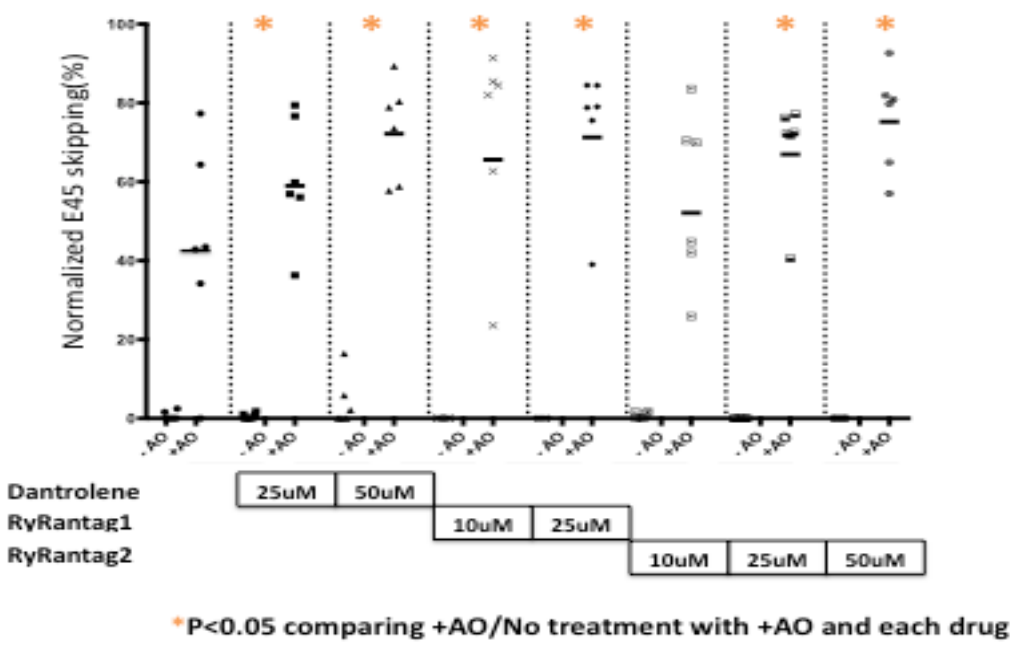

Figure 1. RyRantags boost exon 45 skippping iDRMs (inducible directly reprogrammable myotubes) were seeded at 200,000 cells per well in fibroblast growth media (DMEM (+phenol red, high glucose) + 15% Fetal Bovine Serum (FBS) + 1% Nonessential amino acids + 1% pen/strep) in 6-well plates (Corning) pre-coated for 1 hour with 0.1% gelatin (sigma). The following day, 5μM 4OH-tamoxifen (Sigma; resuspended in ethanol) was added in fibroblast growth media for 24 hours. On day 3, cells were washed in 1 x Phosphate Buffered Saline (PBS; Invitrogen), and fusion media containing 1μM 4OH-tamoxifen was added (1:1 Ham's F-10:DMEM (phenol red free, high glucose), 2% Horse Serum, 2% Insulin-Transferrin-Selenium). On Day 4, cells were transfected with 2-O-methyl AO (MWG Operon) using oligofectamine (life technologies) according to the manufacturer protocol. AO was removed on the following day, cells were washed with 1XPBS, and fresh fusion media containing 1μM 4OH-tamoxifen was added with titrating concentrations of drug and carrier controls. Forty-eight hours later, cell pellets were harvested and frozen for subsequent RNA isolation and exon skipping analysis via nested PCR with primers encompassing the deleted region.

. *P<0.05 P values reflect a Students t test. Bars represent means of two experiments with all conditions run as triplicates.

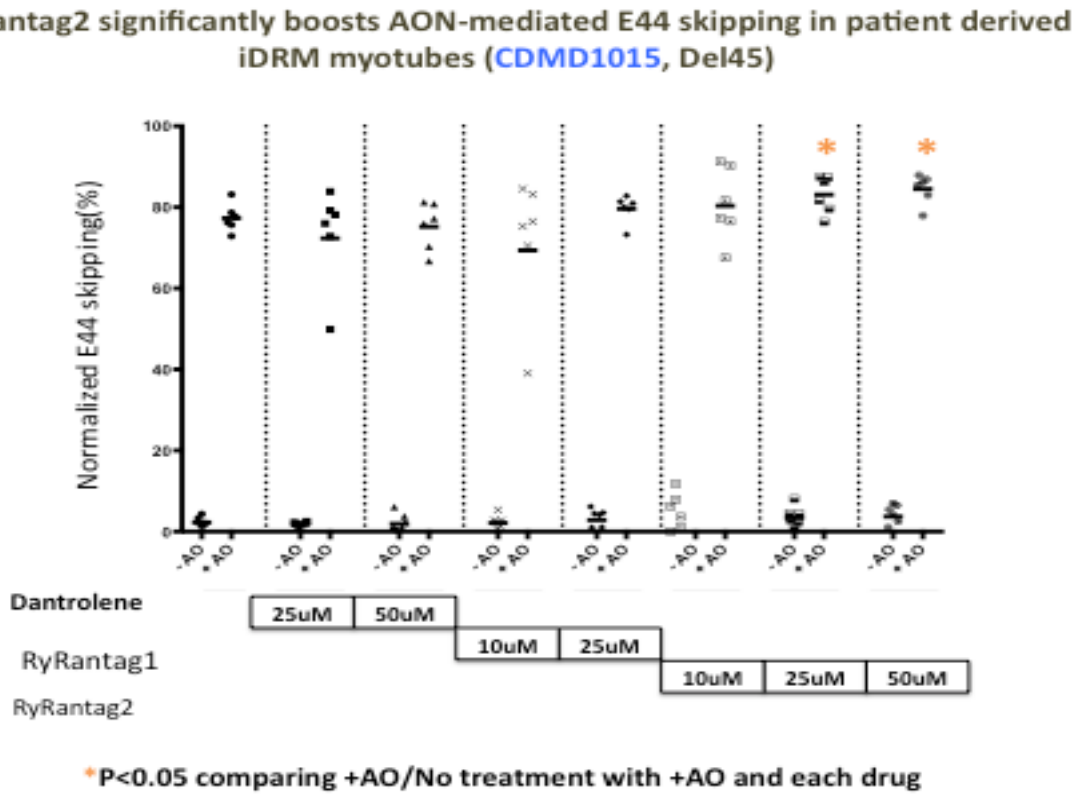

Figure 2. We have tested the antisense oligonucleotide H44A (Wilton et al 2007) in the CDMD1015 (delta 45) cell line. Dose escalation treatment (125, 250, 500 or 1000nM of AO) with or without Dantrolene at 50nM to determine which dose of AO was giving us the best boost. Based on these studies, in this experiement we used 250nM of antisense oligonucleotides with or without dantrolene, RyRantag1 or 2 at indicated concentration.– AO : conditions without the AO + AO: conditions with AO. *P<0.05 P values reflect a Students t test. Bars represent means of two experiments with all conditions run as triplicates.

Milestones Achieved

Prioritize 2 iDRM most sensitive to RyR antags for RNASeQ (18 months; 70% complete)

We are in the process of prioritizing based on initial findings. As of now CDMD1003 exon 45 skipping appears be the most sensitive to RyR boost. We have additionally tentatively prioritized CDMD1089 shown to have endogenous skip activity in response to boost. We will continue testing remaining iDRM and if one shows greater sensitivity, we will re-prioritize. We are on track to achieve this milestone.

Determine relative efficacies of Dantrolene and other calcium modulators for synergizing with AON to promote e51, e44, e45, and e53 skipping (36 months; 50%). We have demonstrated that, like Dantrolene, both other RyRantags tested can boost exon skipping. We have demonstated this in e44,45 and partially in e51 skippable iDRM. In some assays the novel RyRantags are more efficient than dantrolene, though dose side by side dose responses on multiple cells are underway.

HRPO/ACURO Approval

Specific Aim 2
Major Task 1 - Testing RyR pathway antags for activity on DMD patient with suspected propensity to skip.

Subtask 1 - Test compounds on 44 skippable cells for activity in absence of AON (6-36 months; 65%

complete).

We have tested patient derived cells with mutations amenable exon 44 skipping to correct reading frame. It has been suggested that boys with these mutations have a milder disease course due to an increased propensity to constitutively skip exon 44 to produce low levels of dystrophin.

We find that some patient derived exon 44 skippable reprogrammed lines demonstrate increased levels of endogenous exon 44 skipping to restore reading frame (Fig 3). Further, preliminary findings indicate that RyR antags can boost this endogenous exon 44 skipping in the absence of AON in some patient cells (not shown). We continue to screen additional exon 44 skippable patient cells and to establish optimal dosing and conditions for maximal skip boosting activity. We are on target for completion within 36 months.

Subtask 2 - Develop skipping conditions and readouts for skipping exons 44 , 45 and 53 in patient derived cells (6-18 months 90% complete).

This task has been largely completed though efforts are underway to further increase sensitivity and reproducibility of triplicate samples. Conditions and readouts have been developed for exons 44 and 45, but not fully for 53 yet.

Subtask 3 - Test compounds on exon 30, 31, 32 skippable lines (18-32 months, 30% complete).

These lines are derived from patients with a mild phenotype and/or other reasons to suspect endogenous skipping. We have already initiated these studies and preliminary data indicate that the exon 30 and 32 skippable line tested do exhibit high levels of endogenous skipping, as hypothesized, and some demonstrate increased skipping in the context of RyR antags even without AON. We are in the process of reproducing these findings and extending this analysis to additional patient cells. These findings when validated will be significant because dantrolene is already FDA approved and can be used in the absence of AON in these rare mutations that will be unlikely to have effective skipping AON developed in the next few years. Further, dantrolene is much less expensive and more readily available than skipping AON.

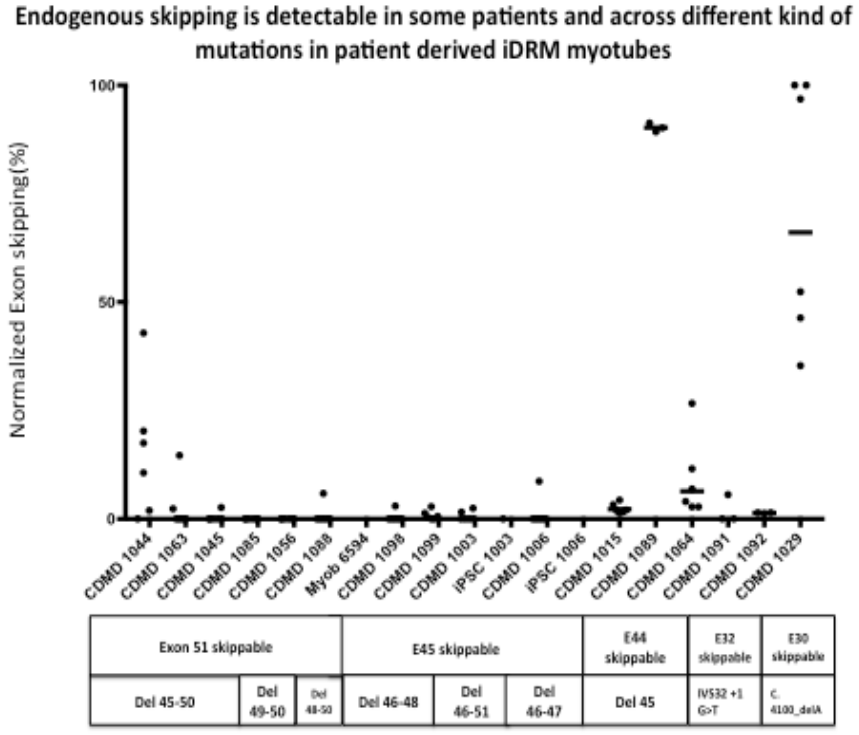

Fig 3. Some iDRM from patients identified as mild phenotypes do show a propensity to skip. Levels of endogenous skip message were identified for 45, 44and 51 skips as in Figures 1 and 2. Primers were identified for described in Figs 1 and 2. Specific primers were developed for detection of exons 30 and 31 and 32 skips.

Milestone Achieved:

Identify iDRM with mutations amenable to skipping by RyR antag alone (month 36, 30% complete).

We have identified several iDRM with some degree of autoskip (Fig. 3). We hypothesize that RyRantags may boost endogenous skipping further in response to RyR antags alone. Initial studies indicate some boost in at least some of the lines identified. Additional testing will allow us to repeat our preliminary findings and expand testing to addition lines predisposed to autoskip.

Specific Aim 3

Major Task 1 - Using chemical genomics and RNA seek to identify skip regulatory pathways and targetable effectors

Subtask 1 - Probe RyR/Ca2+ pathway components with known inhibitors or readouts to establish relationships between effectors and skipping activity (6 months).

We have initiated these experiments. However, culture conditions in the context CAM kinase inhibitors appear to interfere with muscle cell development and survival in the context of reprogramming and differentiating patient derived myotubes and/or induce cell death. We are working to perfect conditions that would enable us to appropriately execute and interpret findings. We are also switching to a different iDRM in the event that the cell we have been working is particularly susceptible to effects o the inhibitors. It is unclear that we will succeed using this approach and may need turn to alternate methods such as RNAi CAMK knockdown or overexpression.

Milestone Achieved: Identification of candidate regulatory pathway skipping (6 months).

This milestone was not reached due to unanticipated drug toxicity.

Major Task 2 - Use RNA Seq, pathway and regulatory sequence analysis

Subtask 1 - Optimize alternate splicing assay using exon capture and RNASeq (12 months, 80% complete). Additionally, we have begun optimizing the exon capture and performed preliminary RNASeq experiments as described using exon capture.

Subtask 2 - High depth RNASeQ on compound treated versus untreated iDRM (deep analysis in repeat experiments with 2 different iDRM most sensitive to RyR pathway antag boost; 18 months, 50% complete).

We have performed high depth sequencing on one pair of treated versus untreated iDRM. We are in the process of analyzing these data and identifying the second iDRM for analysis.

Subtask 3 - Exon-intron motif and transcriptional pathway analysis based on RNASeQ and candidate regulatory motifs identified in Aims 1 and 2 (12-24 months; 0% complete).

We have yet to initiate these studies. Once analysis of initial treated and untreated iDRM pair is complete we will be able to initiate these studies. We are on track to complete these experiments within the projected timeframe.

Subtask 4 - Test candidate pathway effector activity patient derived cell(s) (24-36 months).

We have yet to initiate these studies. Once analysis of initial treated and untreated iDRM is complete we will be able to initiate these studies. We are on track to complete these experiments within the projected timeframe.

What opportunities for training and professional development has the project provided?

These studies have served as a professional development opportunity for trainees Derek Wang, PhD candidate (anticipated graduation 2017) and postdoctoral fellow, Florian Barthelemy, PhD). In addition to providing them with greater technical proficiency working with human DMD models and exon skipping, presentation of initial findings at a poster at the New Directions in Muscle Cell biology meeting has provided presentation training to postdoctoral fellow Florian Barthelemy. Both trainees participate in the CDMD student and post-doctoral training program, which includes presenting and participating in biweekly CDMD inter-group meetings, an annual retreat, and hosting and attending seminars. While not a stated objective of this grant, trainee career development is a major focus of the CDMD.

How were the results disseminated to communities of interest?

Dr. Florian Barthelemy presented a poster reporting initial findings at the New Directions in Muscle Cell biology meeting, 2016.

What do you plan to do during the next reporting period to accomplish the goals?

Over the next year we hope to have completed assay development and refinement for exon 53 skippable cells and to improve reproducibility in the assays. We will expand the number of replicate experiments using iDRM and expand our studies to include additional patient mutations susceptible to skipping 51, 45, 30, 32, 44 or 53. This will help to determine how generalizable our findings are to all skippable mutations, aid in potential future trial design, and will provide tools for assessing the molecular differences between lines determines to be susceptible and non-suscepitible.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Short term: The research completed has lead to a determination of the relevance of exon skipping enhancers to AON-mediated exon skipping in the context of specific patient iDRM and DMD. By testing RyR antags in combination with AONs targeting exons 51, 45, 53, and 44 on a panel of patient-derived myotubes with common *DMD* mutations we have begun to identify which subset of DMD patient populations that might benefit from combination AON/RyR-antag therapy. So far we have identified several patient derived cells with mutation requiring exon 51, 45, or 44 skipping to restore reading frame that are amenable to RyR antag boost. We have begun to establish which of these compounds have the greatest skip boosting activity, thus informing on mutations most appropriate to move into clinical trials in combination with AON. Further, we have begun to develop data to assess if any of these compounds promote additional naturally occurring exon skipping in exon 44 skippble lines and rare patients with small indels or nonsense mutations in ‘in frame’ exons; our findings to date indicate that RyR antag pathway compounds can promote endogenous skipping in some of these DMD patient models. Gathering these data on a small panel of exon 30, 31, 32 mutations, will provide justification for assessment of these compounds ‘off label’ in small patient populations. Upon validation, these findings will open up exon skipping in these patients prior to the development of the mature RNA. We have established that some patient mutations have propensity to auto correct due to endogenous exon skipping and have associated with milder phenotype. In addition, the mechanistic studies may highlight novel and potentially more effective means to enhance exon skipping and second generation agents that can be tested to broaden the impact of exon skipping in DMD.

Long term Impact. We anticipate that there will be substantial long-term gains from the early and proposed research. Exon skipping is a now emerging therapy designed to correct the proximate genetic cause of DMD by inducing the expression of internally truncated protein associated with the much milder BMD. Once optimized it is predicted to significantly benefit up to 80% and enhance quality of life through slowing of disease progression. This will likely extend life directly. However, variation in patient response, suboptimal induction of dystrophin protein and clinical response clearly indicate that additional work is warranted to enhance the therapeutic potential of exon skipping. The work proposed here as adjuvant to exon skipping may make exon skipping more therapeutically beneficial in the years to come. The work here proposed using RyRantags to boost endogenous skippers may enable its use alone therapeutically in a subpopulation of Duchenne patients with particular mutations. This will particularly impactful for rare mutations for which the development of AON is not yet in the development pipeline.

What was the impact on other disciplines?

With the initial successes of AON mediated exon skipping in DMD, RNA splice modulation technology is being applied to several rare diseases, i.e. SMA, myotonic dystrophy and others. Compounds demonstrated to boost DMD exon skipping alone or in the context of AON in DMD represent prime candidates to asses for splice altering activity in other disease setting.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Our findings promise to provide the public knowledge regarding exon skipping and RNA therapeutics.

5. CHANGES/PROBLEMS

Nothing to Report

6. PRODUCTS

Publications, conference papers, and presentations

Dr. Florian Barthelemy presented a poster reporting initial findings at the New Directions in Muscle Cell biology meeting, 2016.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: M. Carrie Miceli
Project Role: PI
Researcher Identifier (e.g., ORCID ID): NA
Nearest person month worked: 1 cal mos
Contribution to Project: PI Dr. Miceli oversees all experiments helps with data interpretation and data publication.

Name: Stanley Nelson
Project Role: Co-I

Researcher Identifier (e.g., ORCID ID): NA
Nearest person month worked: 1 cal mos
Contribution to Project: Dr Nelson is an expert in RNAseq and DMD genotype phenotype correlations. He advises us on aims 1-2 and is key to the execution of Aim3.

Name Florian Barthelemy
Project Role: Post Doctoral Fellow
Nearest person month worked: 3 cal mos
Contribution to Project: Florian Barthelemy: (post-doctoral fellow, Miceli lab) has taken the lead on developing all of the skipping reagents and performing assays assessing Rycal skip activity in a number of patient derived cells.

Name: Derek Wang
Project Role: Graduate Research Student
Nearest person month worked: 2 cal mos
Contribution to Project: Mr. Wang has assisted Dr. Barthelemy on assay development, ddPCR studies, patient cell banking reprogramming and differentiation.

Name: Ekaterina Mokhonova
Project Role: Staff Research Assistant
Nearest person month worked: 9 cal mos
Contribution to Project has been involved in banking cells and assessing pathway inhibitors in patient derived cells.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes – please see Other Support page

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

9. APPENDICES

Nothing to Report

OTHER SUPPORT

MICELI, M. CARRIE, Ph.D.

PREVIOUSLY ACTIVE GRANT HAS CLOSED

CIRM TRX-05426 3/1/2013- 2/28/2015 3.6 cal months
PI: Stanley Nelson; Co-PI: M. Carrie Miceli $337,542 (Direct Costs)
Title: Combination Therapy to Enhance AntiSense Mediated Exon Skipping for Duchene Muscular Dystrophy
Major Goals: To perform all preclinical assessment, dose ranging and efficacy and toxicology studies required to enable IND application and 100% clinical trial readiness for a combined therapeutic CDMD51Plus for use in exon skipping for DMD. Dr. Miceli will oversee all UCLA preclinical studies.

Penn/UCLA Wellstone Center Grant 7/01/10-6/30/15 0.6 cal months
PI: Lee Sweeney, University of Pennsylvania $34,724 (Direct Costs)
Co-PIs/collaborators:Drs. McNally, Univ. of Chicago; Walter and Vandenborn; University of Florida; Spencer, Miceli, Nelson, UCLA and Ostap and Finkel, Penn
Title: Failed Regeneration in the Muscular Dystrophies: Inflammation, Fibrosis and Fat
Major Goals: As a collaborator with Dr. Spencer (subcontract PI), we examine the immune response to anti-fibrotic therapies.

UCLA Broad Stem Cell Research Center 8/25/14-8/24/15 1.2 cal months
Innovator Award $50,000 (Direct Costs)
PI: M. Carrie Miceli
Major Goals: This award is to recognize and enable pursuit of Stem Cell Approaches to Combination Exon Skipping.

ACTIVE

P30 AR057230-06 4/1/14-3/31/19 1.2 cal months
NIH/NIAMS $80,000 (Direct Costs)
PI: M. Spencer; Co-PI: M. C. Miceli
UCLA Muscular Dystrophy Core Center
(Miceli: Director of the High Throughput Screening and Cell Repository Core B and Member of the Executive Committee Core A). The goal of this grant is to establish a Muscular Dystrophy Center on the UCLA campus, consisting of research cores, pilot and feasibility funding and an administrative core that will facilitate translational research in the area of muscular dystrophy.

University of Florida, 8/01/15-7/30/20 0.6 cal months
PI: Lee Sweeney, site PI M. Spencer $22,000 (Direct Costs)
Title: Failed Regeneration in the Muscular Dystrophies: Inflammation, Fibrosis and Fat
Major Goals: Examination of the immune response in the context of anti-fibrotic therapies.

R01 AR048177 9/01/15-8/30/20 0.6 cal months
NIH $20,000 (Direct Costs)
PI: M. Spencer
Title: Mechanisms Underlying Limb Girdle Muscular Dystrophy 2A Due to Calpain 3 Mutations
Major Goals: To bank fibroblasts and reprogram iDRM from LCM2A patients

OTHER SUPPORT

NELSON, STANLEY F.

PREVIOUSLY ACTIVE GRANT HAS CLOSED

PPMD (PI:Nelson) 2/01/2013-01/31/2014 0.3 CM
Title: Pilot Project to Identify Genetic Modifiers of Duchenne Muscular Dystrophy $95,266/y
To identify novel genetic modifiers of disease progression using a search through the entire human genome for naturally occurring common and rare protein coding variants that modify the progression of muscular dystrophy in humans with DMD location mutations predicted to cause complete loss of function.

PPMD (Nelson) 01/01/2011-12/31/2015 0.6 CM
Title: RNA_SEQ Analysis for Modifiers of Fibrosis $52,500/y
This project is funded by PPMD and is integrated into the UPENN/UChicago/UCLA/UF Wellstone Center to perform RNA_SEQ experiments to assess modulators of fibrosis in mice.

TRX-05426 (PI: Nelson, Co-PI: Miceli) 3/1/2013- 2/28/2015 3.6 CM
California Institute for Regenerative Medicine (CIRM) $374,913/y
Title: Combination Therapy to Enhance AntiSense Mediated Exon Skipping for Duchene Muscular Dystrophy
To perform all preclinical assessment, dose ranging and efficacy and toxicology studies required to enable IND application and 100% clinical trial readiness for a combined therapeutic CDMD51Plus for use in exon skipping for DMD.

ACTIVE

P30 AR057230-01 (Spencer) 04/01/2014-03/31/2019 1.2 CM
NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) $84,373/y
UCLA Muscular Dystrophy Core Center
Center will provide support for muscular dystrophy research center.

1R01NS073871-01A1 (Nelson) 09/01/2011-08/31/2017 2.4 CM
NIH/NINDS $488,500/y
Title: Rapid Phenotyping for Rare Variant Discovery in Autism
This project is intended to use web-based recruiting to greatly expand DNA samples available for genetic analysis to determine the heterogeneous genetic causes of autism.

NIH 1U01HG007703-01 (MPI) 4/01/14-3/31/18 1.2 CM
(E. Vilain, C. Palmer, K. Dipple, S Nelson MPI) $4,661,458
Title: UCLA Undiagnosed Diseases Network Sequencing
PI will administer and direct clinical assessment and genetic mutation analysis of subjects with rare diseases.

PENDING

None